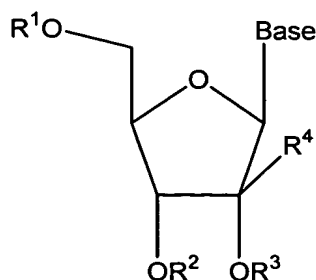


WE CLAIM:

1. A pharmaceutical composition effective for the treatment of a *Flaviviridae* infection in a host, comprising an effective amount of a 2'-branched nucleoside, or pharmaceutically acceptable prodrug and/or salt thereof, optionally in a pharmaceutically acceptable carrier or diluent, in combination with one or more drugs that directly or indirectly induce a mutation in a *Flaviviridae* at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT, of domain B of the RNA polymerase region, and/or one or more drugs that are associated with such a mutation.
2. The pharmaceutical composition of claim 1 wherein the drug is drug that directly or indirectly induces or is associated with a mutation in a *Flaviviridae* at a location other than nucleotide 1214 (G to C) or 405 Ser to Thr of the RNA polymerase region of BVDV or nucleotide 8443 (G to C) of the HCV genome or 282 Ser to Thr of the RNA polymerase region of HCV.
3. A pharmaceutical composition effective for the treatment of a *Flaviviridae* infection in a host, comprising an effective amount of a 2'-branched nucleoside, or pharmaceutically acceptable prodrug and/or salt thereof, optionally in a pharmaceutically acceptable carrier or diluent, in combination with interferon.
4. The pharmaceutical composition of claim 3, wherein the interferon is selected from the group consisting of Intron-A (interferon alpha-2b), PEG-INTRON (pegylated interferon alpha-2b), Roferon-A (interferon alfa-2a), PEGASYS (pegylated interferon alfa-2a), INFERGEN (interferon alfacon-1), OMNIFERON (natural interferon), ALBUFERON, REBIF (interferon beta-1a), Omega Interferon, Oral Interferon Alpha, and Interferon gamma-1b.
5. The pharmaceutical composition of any one of claims 1-4, wherein the 2'-branched nucleoside is a 2'-branched pyrimidine nucleoside.

6. The pharmaceutical composition of claim 5, wherein the 2'-branched nucleoside is β -D-2'-CH₃-riboC.
7. The pharmaceutical composition of claim 5, wherein the 2'-branched nucleoside is a 3'-amino acid prodrug of β -D-2'-CH₃-riboC.
- 5 8. The pharmaceutical composition of claim 7, wherein the 2'-branched nucleoside is 3'-L-valinyl prodrug of β -D-2'-CH₃-riboC.
9. The pharmaceutical composition of any one of claims 1-4, wherein the 2'-branched nucleoside is a 2'-branched purine nucleoside.
- 10 10. The pharmaceutical composition of claim 9, wherein the 2'-branched nucleoside is β -D-2'-CH₃-riboA.
11. The pharmaceutical composition of claim 9, wherein the 2'-branched nucleoside is a 3'-amino acid prodrug of β -D-2'-CH₃-riboA.
12. The pharmaceutical composition of claim 11, wherein the 2'-branched nucleoside is a 3'-L-valinyl prodrug of β -D-2'-CH₃-riboA.
- 15 13. The pharmaceutical composition of claim 9, wherein the 2'-branched nucleoside is β -D-2'-CH₃-ribo-6-N-methylaminopurine.
14. The pharmaceutical composition of claim 9, wherein the 2'-branched nucleoside is a 3'-amino acid prodrug of β -D-2'-CH₃-ribo-6-N-methylaminopurine.
- 20 15. The pharmaceutical composition of claim 14, wherein the 2'-branched nucleoside is a 3'-L-valinyl prodrug of β -D-2'-CH₃-ribo-6-N-methylaminopurine.

16. The pharmaceutical compositions of any one of claims 1-4, wherein the 2'-branched nucleoside is of the formula:



or its pharmaceutically acceptable prodrug and/or salt, wherein

R^1 , R^2 , and R^3 are independently H, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester (including alkyl or arylalkyl sulfonyl including methanesulfonyl); benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; lipid (including a phospholipid); amino acid; carbohydrate; peptide; cholesterol; or a pharmaceutically acceptable leaving group that provides a compound wherein R^1 , R^2 or R^3 is independently H or phosphate when administered *in vivo*; and

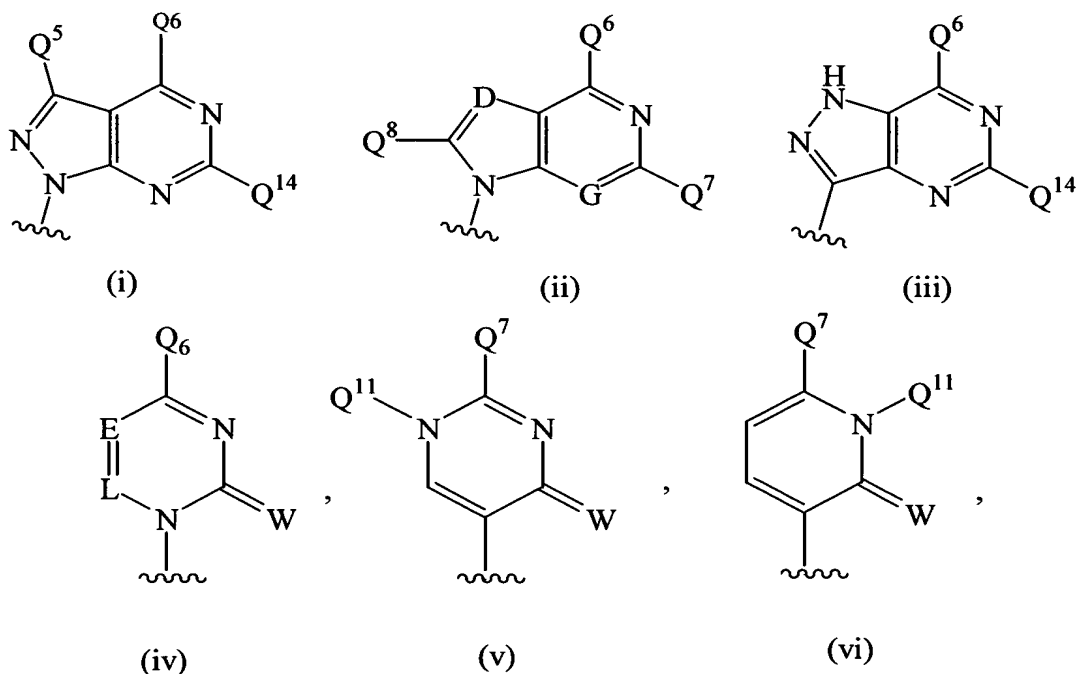
R^4 is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, $-C(O)O(\text{alkyl})$, $-C(O)O(\text{lower alkyl})$, $-O(\text{acyl})$, $-O(\text{lower acyl})$, $-O(\text{alkyl})$, $-O(\text{lower alkyl})$, $-O(\text{alkenyl})$, chloro, bromo, fluoro, iodo, NO_2 , NH_2 , $-\text{NH}(\text{lower alkyl})$, $-\text{NH}(\text{acyl})$, $-\text{N}(\text{lower alkyl})_2$, or $-\text{N}(\text{acyl})_2$;

and Base is a purine or pyrimidine.

17. The pharmaceutical composition of claim 16, wherein base is selected from the group consisting of adenine, N^6 -alkylpurines, N^6 -acylpurines (wherein acyl is $\text{C(O)}(\text{alkyl, aryl, alkylaryl, or arylalkyl})$, N^6 -benzylpurine, N^6 -halopurine, N^6 -vinylpurine, N^6 -acetylenic purine, N^6 -acyl purine, N^6 -hydroxyalkyl purine, N^6 -thioalkyl purine, N^2 -alkylpurines, N^2 -alkyl-6-thiopurines, thymine, cytosine, 5-fluorocytosine, 5-methylcytosine, 6-azapyrimidine, including 6-azacytosine, 2-and/or 4-mercaptopyrimidine, uracil, 5-halouracil, including 5-fluorouracil, C^5 -alkylpyrimidines, C^5 -benzylpyrimidines, C^5 -halopyrimidines, C^5 -vinyl-

pyrimidine, C⁵-acetylenic pyrimidine, C⁵-acyl pyrimidine, C⁵-hydroxyalkyl purine, C⁵-amidopyrimidine, C⁵-cyanopyrimidine, C⁵-nitropyrimidine, C⁵-aminopyrimidine, N²-alkylpurines, N²-alkyl-6-thiopurines, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl.

18. The pharmaceutical composition of claim 16, wherein base is of the formula:



wherein:

G and L are each independently CH or N;

D is N, CH, C-CN, C-NO₂, C-C₁₋₃ alkyl, C-NHCONH₂, C-CONQ¹¹Q¹¹, C-CSNQ¹¹Q¹¹, CCOOQ¹¹, C-C(=NH)NH₂, C-hydroxy, C-C₁₋₃alkoxy, C-amino, C-C₁₋₄alkyl-amino, C-di(C₁₋₄ alkyl)amino, C-halogen, C-(1,3-oxazol-2-yl), C-(1,3-thiazol-2-yl), or C-(imidazol-2-yl); wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboxy, and C₁₋₃ alkoxy;

E is N or CQ⁵;

W is O, S, or NR;

R is H, OH, alkyl;

Q^6 is H, OH, SH, NH_2 , C_{1-4} alkylamino, $di(C_{1-4}$ alkyl)amino, C_{3-6} cycloalkylamino, halogen,

C_{1-4} alkyl, C_{1-4} alkoxy, or CF_3 ;

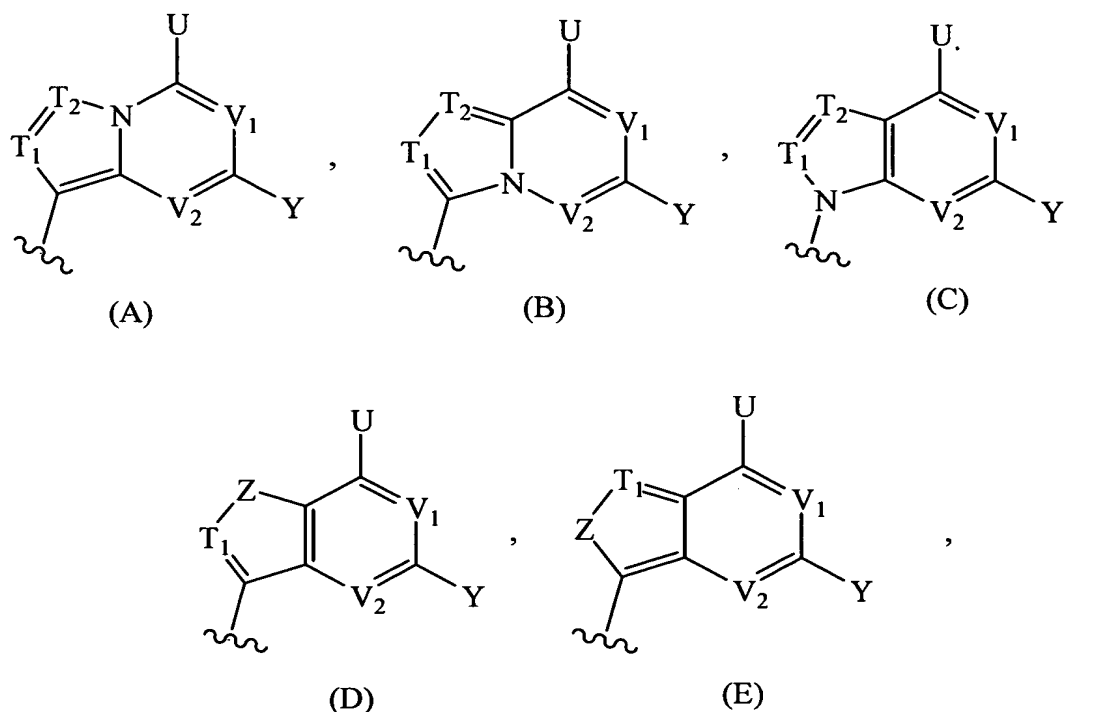
5 Q^5 is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} alkylamino, CF_3 , halogen, N, CN, NO_2 , $NHCONH_2$, $CONQ^{11}Q^{11}$, $CSNQ^{11}Q^{11}$, $COOQ^{11}$, $C(=NH)NH_2$, hydroxy, C_{1-3} alkoxy,amino, C_{1-4} alkylamino, $di(C_{1-4}$ alkyl)amino, halogen, 1,3-oxazol-2-yl, 1,3-thiazol-2-yl, or imidazol-2-yl; wherein alkyl is
10 unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboxy, and C_{1-3} alkoxy;

Q^7 and Q^{14} are each independently selected from the group consisting of H, CF_3 , OH, SH, OR, SR C_{1-4} alkyl, amino, C_{1-4} alkylamino, C_{3-6} cycloalkylamino, and $di(C_{1-4}$ alkyl)amino;

Q^{11} is independently H or C_{1-6} alkyl; and

15 Q^8 is H, halogen, CN, carboxy, C_{1-4} alkyloxycarbonyl, N_3 , amino, C_{1-4} alkylamino, $di(C_{1-4}$ alkyl)amino, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, $(C_{1-4}$ alkyl) $_{0-2}$ aminomethyl, NH_2 , CN, NO_2 , C_{1-3} alkyl, $NHCONH_2$, $CONQ^{11}Q^{11}$, $CSNQ^{11}Q^{11}$, $COOQ^{11}$, $C(=NH)NH_2$, 1,3-oxazol-2-yl, 1,3-thiazol-2-yl, or imidazol-2-yl, wherein alkyl is unsubstituted or
20 substituted with one to three groups independently selected from halogen, amino, hydroxy, carboxy, and C_{1-3} alkoxy.

19. The pharmaceutical composition of claim 16, wherein base is of the formula:



wherein:

- 5 T_1 and T_2 are independently selected from N, CH, or C- Q^{16} ;
- Q^{16} , U, and Y are independently selected from is H, OH, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, cycloalkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, OR^4 , NR^4R^5 or SR^5 , Br-vinyl, -O-alkyl, -O-alkenyl, -O-alkynyl, -O-aryl, -O-aralkyl, -O-acyl, -O-cycloalkyl, NH_2 , NH-alkyl, N-dialkyl, NH-acyl, N-aryl, N-aralkyl, NH-cycloalkyl, SH, S-alkyl, S-acyl, S-aryl, S-cycloalkyl, S-aralkyl, CN, N_3 , COOH, $CONH_2$, CO_2 -alkyl, $CONH$ -alkyl, CON -dialkyl, OH, CF_3 , CH_2OH , $(CH_2)_mOH$, $(CH_2)_mNH_2$, $(CH_2)_mCOOH$, $(CH_2)_mCN$, $(CH_2)_mNO_2$, $(CH_2)_mCONH_2$, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{3-6} cycloalkylamino, C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl, C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, $(C_{1-4}$ alkyl) $_{0-2}$ aminomethyl, or -NHC(=NH) NH_2 ;
- 10
- 15

R^4 and R^5 are independently selected from hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl);

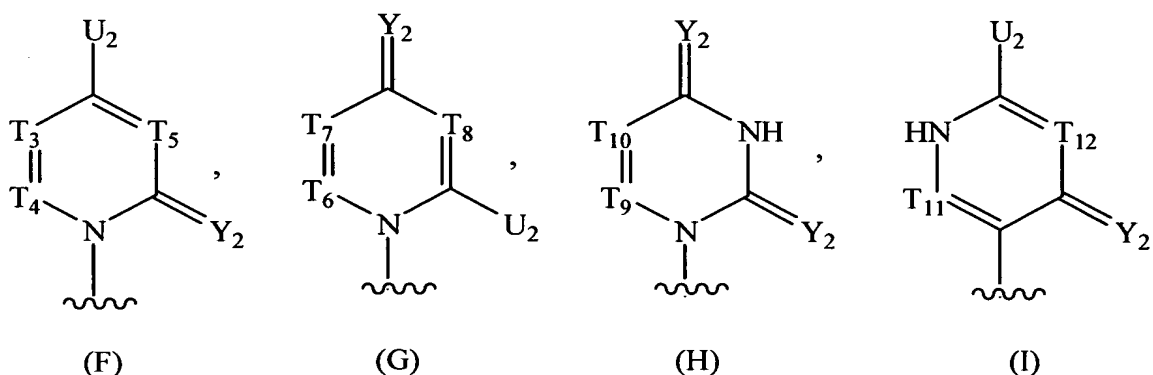
m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

Z is S, SO, SO₂, C=O, or NQ²⁰;

5 Q^{20} is H or alkyl; and

V_1 and V_2 are independently selected from CH or N.

20. The pharmaceutical composition of claim 16, wherein base is of the formula:



10 wherein:

T_3 and T_4 are independently selected from N or CQ²²;

Q^{22} is independently selected from H, OH, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, cycloalkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, OR⁴, NR⁴R⁵ or SR⁵, Br-vinyl, -O-alkyl, -O-alkenyl, -O-alkynyl, -O-aryl, -O-aralkyl, -O-acyl, -O-cycloalkyl, NH₂, NH-alkyl, N-dialkyl, NH-acyl, N-aryl, N-aralkyl, NH-cycloalkyl, SH, S-alkyl, S-acyl, S-aryl, S-cycloalkyl, S-aralkyl, CN, N₃, COOH, CONH₂, CO₂-alkyl, CONH-alkyl, CON-dialkyl, OH, CF₃, CH₂OH, (CH₂)_mOH, (CH₂)_mNH₂, (CH₂)_mCOOH, (CH₂)_mCN, (CH₂)_mNO₂, (CH₂)_mCONH₂, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, C₃₋₆ cycloalkylamino, C₁₋₄ alkoxy, C₁₋₄ alkoxycarbonyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulfonyl, (C₁₋₄ alkyl)₀₋₂aminomethyl, or -NHC(=NH)NH₂;

T_5 is NH;

R⁴ and R⁵ are independently selected from hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl);

m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

T₆, T₇, T₈, T₉, T₁₀, T₁₁, and T₁₂ are independently selected from N or CH;

5 U₂ is H, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, OR⁴, NR⁴R⁵ or SR⁵;

Y₂ is O, S, NH, NR or CQ²⁴Q²⁶ where R is H, OH, or alkyl; and

10 Q²⁴ and Q²⁶ are independently selected from H, alkyl, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, OR⁴, NR⁴R⁵ or SR⁵.

21. A pharmaceutical composition effective for the treatment of a *Flaviviridae* infection in a host, comprising:

15 an effective amount of a 2', 3' and/or 5'-prodrug of a 2'-branched nucleoside, or pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier or diluent;

20 in combination with one or more drugs that directly or indirectly induce a mutation in a *Flaviviridae* at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT, of domain B of the RNA polymerase region, and/or one or more drugs that are associated with such a mutation.

22. The pharmaceutical composition of claim 21 wherein the 2', 3' and/or 5'-prodrug of a 2'-branched nucleoside is a 2', 3' and/or 5'-prodrug of a 2'-branched pyrimidine nucleoside.

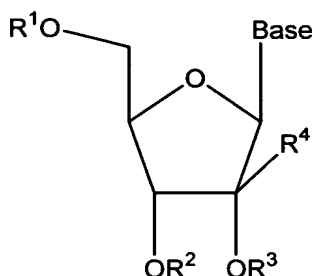
25 23. The pharmaceutical composition of claim 22 wherein the 2', 3' and/or 5'-prodrug of a 2'-branched nucleoside is 2', 3' and/or 5'-prodrug of β-D-2'-CH₃-riboC.

24. The pharmaceutical composition of claim 23 wherein the 2', 3' and/or 5'-prodrug of a 2'-branched nucleoside is 3'-amino acid prodrug of β-D-2'-CH₃-riboC.

25. The pharmaceutical composition of claim 24 wherein the 2', 3' and/or 5'-prodrug of a 2'-branched nucleoside is 3'-L-valinyl prodrug of β -D-2'-CH₃-riboC.
26. The pharmaceutical composition of claim 21 wherein the 2', 3' and/or 5'-prodrug of a 2'-branched nucleoside is a 2', 3' and/or 5'-prodrug of a 2'-branched purine nucleoside.
27. The pharmaceutical composition of claim 26 wherein the 2', 3' and/or 5'-prodrug of a 2'-branched nucleoside is 2', 3' and/or 5'-prodrug of β -D-2'-CH₃-riboA.
28. The pharmaceutical composition of claim 27 wherein the 2', 3' and/or 5'-prodrug of a 2'-branched nucleoside is 3'-amino acid prodrug of β -D-2'-CH₃-riboA.
29. The pharmaceutical composition of claim 28 wherein the 2', 3' and/or 5'-prodrug of a 2'-branched nucleoside is 3'-L-valinyl prodrug of β -D-2'-CH₃-riboA.
30. The pharmaceutical composition of claim 26 wherein the 2', 3' and/or 5'-prodrug of a 2'-branched nucleoside is 2', 3' and/or 5'-prodrug of β -D-2'-CH₃-ribo-6-N-methylamino-purine.
31. The pharmaceutical composition of claim 30 wherein the 2', 3' and/or 5'-prodrug of a 2'-branched nucleoside is 3'-amino acid prodrug of β -D-2'-CH₃-ribo-6-N-methylamino-purine.
32. The pharmaceutical composition of claim 31 wherein the 2', 3' and/or 5'-prodrug of a 2'-branched nucleoside is 3'-L-valinyl prodrug of β -D-2'-CH₃-ribo-6-N-methylamino-purine.
33. A method for treating a *Flaviviridae* infection in a host, comprising administering an effective amount of a 2'-branched nucleoside, or its pharmaceutically acceptable prodrug or salt to the host, optionally in a pharmaceutically acceptable carrier or diluent, in combination and/or alternation with one or more drugs that directly or indirectly induce a mutation in a *Flaviviridae* at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence, XXXSGXXXT, of domain B of the RNA polymerase region, and/or one or more drugs that are associated with such a mutation.

34. The method of claim 33 wherein the drug is drug that directly or indirectly induces or is associated with a mutation in a *Flaviviridae* at a location other than nucleotide 1214 (G to C) or 405 Ser to Thr of the RNA polymerase region of BVDV or nucleotide 8443 (G to C) of the HCV genome or 282 Ser to Thr of the RNA polymerase region of HCV.
35. A method for treating a *Flaviviridae* infection in a host comprising administering an effective amount of a 2'-branched nucleoside, or pharmaceutically acceptable prodrug and/or salt thereof to the host, optionally in a pharmaceutically acceptable carrier or diluent, in combination and/or alternation with interferon.
36. The method of claim 35, wherein the interferon is selected from the group consisting of Intron-A (interferon alpha-2b), PEG-INTRON (pegylated interferon alpha-2b), Roferon-A (interferon alfa-2a), PEGASYS (pegylated interferon alfa-2a), INFERGEN (interferon alfacon-1), OMNIFERON (natural interferon), ALBUFERON, REBIF (interferon beta-1a), Omega Interferon, Oral Interferon Alpha, and Interferon gamma-1b.
37. The method of any one of claims 33-36, wherein the 2'-branched nucleoside is a 2'-branched pyrimidine nucleoside.
38. The method of claim 37, wherein the 2'-branched nucleoside is β -D-2'-CH₃-riboC.
39. The method of claim 37, wherein the 2'-branched nucleoside is a 3'-amino acid prodrug of β -D-2'-CH₃-riboC.
40. The method of claim 39, wherein the 2'-branched nucleoside is 3'-L-valinyl prodrug of β -D-2'-CH₃-riboC.
41. The method of any one of claims 33-36, wherein the 2'-branched nucleoside is a 2'-branched purine nucleoside.
42. The method of claim 41, wherein the 2'-branched nucleoside is β -D-2'-CH₃-riboA.
43. The method of claim 41, wherein the 2'-branched nucleoside is a 3'-amino acid prodrug of β -D-2'-CH₃-riboA.

44. The method of claim 43, wherein the 2'-branched nucleoside is a 3'-L-valinyl prodrug of β -D-2'-CH₃-riboA.
45. The method of claim 41, wherein the 2'-branched nucleoside is β -D-2'-CH₃-ribo-6-N-methylaminopurine.
- 5 46. The method of claim 41, wherein the 2'-branched nucleoside is a 3'-amino acid prodrug of β -D-2'-CH₃-ribo-6-N-methylaminopurine.
47. The method of claim 46, wherein the 2'-branched nucleoside is a 3'-L-valinyl prodrug of β -D-2'-CH₃-ribo-6-N-methylaminopurine.
48. The method of any one of claims 33-36, wherein the 2'-branched nucleoside is of the formula:
- 10



or its pharmaceutically acceptable prodrug and/or salt, wherein

R^1 , R^2 , and R^3 are independently H, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester (including alkyl or arylalkyl sulfonyl including methanesulfonyl); benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; lipid (including a phospholipid); amino acid; carbohydrate; peptide; cholesterol; or a pharmaceutically acceptable leaving group that provides a compound wherein R^1 , R^2 or R^3 is independently H or phosphate when administered *in vivo*; and

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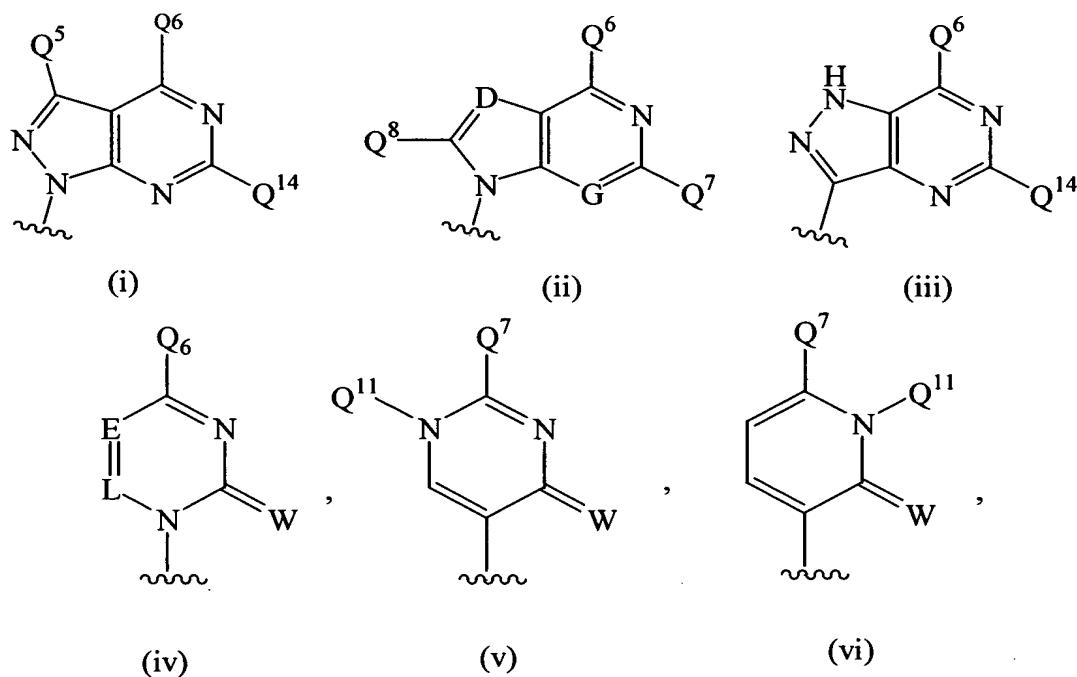
R^4 is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, NO₂, NH₂, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)₂, or -N(acyl)₂;

25

and Base is a purine or pyrimidine.

49. The method of claim 48, wherein base is selected from the group consisting of adenine, N⁶-alkylpurines, N⁶-acylpurines (wherein acyl is C(O)(alkyl, aryl, alkylaryl, or arylalkyl), N⁶-benzylpurine, N⁶-halopurine, N⁶-vinylpurine, N⁶-acetylenic purine, N⁶-acyl purine, N⁶-hydroxyalkyl purine, N⁶-thioalkyl purine, N²-alkylpurines, N²-alkyl-6-thiopurines, thymine, cytosine, 5-fluorocytosine, 5-methylcytosine, 6-azapyrimidine, including 6-azacytosine, 2- and/or 4-mercaptopyrimidine, uracil, 5-halouracil, including 5-fluorouracil, C⁵-alkylpyrimidines, C⁵-benzylpyrimidines, C⁵-halopyrimidines, C⁵-vinylpyrimidine, C⁵-acetylenic pyrimidine, C⁵-acyl pyrimidine, C⁵-hydroxyalkyl purine, C⁵-amidopyrimidine, C⁵-cyanopyrimidine, C⁵-nitropyrimidine, C⁵-aminopyrimidine, N²-alkylpurines, N²-alkyl-6-thiopurines, 5-azacytidinyl, 5-azauracil, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl.

50. The method of claim 49, wherein base is of the formula:



wherein:

G and L are each independently CH or N;

5 D is N, CH, C-CN, C-NO₂, C-C₁₋₃ alkyl, C-NHCONH₂, C-CONQ¹¹Q¹¹, C-CSNQ¹¹Q¹¹, CCOOQ¹¹, C-C(=NH)NH₂, C-hydroxy, C-C₁₋₃alkoxy, C-amino, C-C₁₋₄alkyl-amino, C-di(C₁₋₄ alkyl)amino, C-halogen, C-(1,3-oxazol-2-yl), C-(1,3-thiazol-2-yl), or C-(imidazol-2-yl); wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboxy, and C₁₋₃ alkoxy;

E is N or CQ⁵;

W is O, S, or NR;

R is H, OH, alkyl;

10 Q⁶ is H, OH, SH, NH₂, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, C₃₋₆ cycloalkylamino, halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, or CF₃;

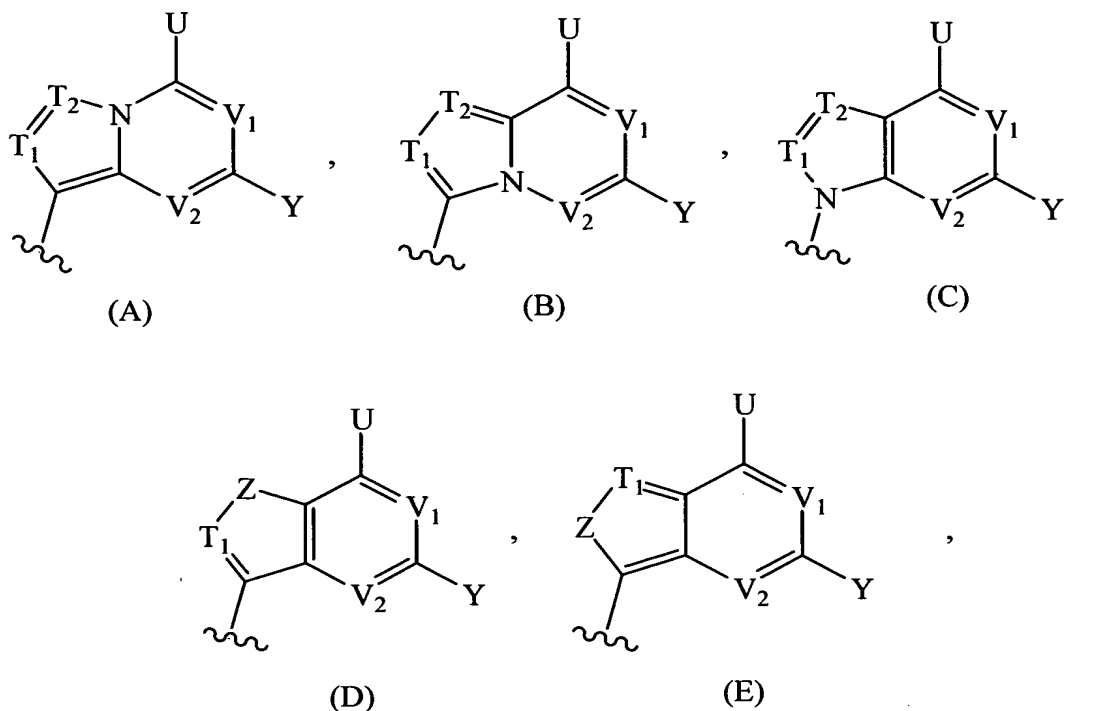
15 Q⁵ is H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₄ alkylamino, CF₃, halogen, N, CN, NO₂, NHCONH₂, CONQ¹¹Q¹¹, CSNQ¹¹Q¹¹, COOQ¹¹, C(=NH)NH₂, hydroxy, C₁₋₃alkoxy, amino, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, halogen, 1,3-oxazol-2-yl, 1,3-thiazol-2-yl, or imidazol-2-yl; wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboxy, and C₁₋₃ alkoxy;

20 Q⁷ and Q¹⁴ are each independently selected from the group consisting of H, CF₃, OH, SH, OR, SR C₁₋₄ alkyl, amino, C₁₋₄ alkylamino, C₃₋₆ cycloalkylamino, and di(C₁₋₄ alkyl)amino;

Q¹¹ is independently H or C₁₋₆ alkyl; and

25 Q⁸ is H, halogen, CN, carboxy, C₁₋₄ alkyloxycarbonyl, N₃, amino, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulfonyl, (C₁₋₄ alkyl)₀₋₂aminomethyl, NH₂, CN, NO₂, C₁₋₃ alkyl, NHCONH₂, CONQ¹¹Q¹¹, CSNQ¹¹Q¹¹, COOQ¹¹, C(=NH)NH₂, 1,3-oxazol-2-yl, 1,3-thiazol-2-yl, or imidazol-2-yl, wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxy, carboxy, and C₁₋₃ alkoxy.

51. The method of claim 49, wherein base is of the formula:



wherein:

5 T_1 and T_2 are independently selected from N, CH, or C- Q^{16} ;

Q^{16} , U, and Y are independently selected from is H, OH, substituted or
 unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or
 unsubstituted alkynyl, cycloalkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl,
 chloro, bromo, fluoro, iodo, OR^4 , NR^4R^5 or SR^5 , Br-vinyl, -O-alkyl, -O-
 alkenyl, -O-alkynyl, -O-aryl, -O-aralkyl, -O-acyl, -O-cycloalkyl, NH_2 , NH-
 alkyl, N-dialkyl, NH-acyl, N-aryl, N-aralkyl, NH-cycloalkyl, SH, S-alkyl, S-
 acyl, S-aryl, S-cycloalkyl, S-aralkyl, CN, N_3 , COOH, $CONH_2$, CO_2 -alkyl,
 CONH-alkyl, CON-dialkyl, OH, CF_3 , CH_2OH , $(CH_2)_mOH$, $(CH_2)_mNH_2$,
 $(CH_2)_mCOOH$, $(CH_2)_mCN$, $(CH_2)_mNO_2$, $(CH_2)_mCONH_2$, C_{1-4} alkylamino,
 di(C_{1-4} alkyl)amino, C_{3-6} cycloalkylamino, C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl,
 C_{1-6} alkylthio, C_{1-6} alkylsulfonyl, $(C_{1-4}$ alkyl) $_{0-2}$ aminomethyl, or
 -NHC(=NH) NH_2 ;

R^4 and R^5 are independently selected from hydrogen, acyl (including lower acyl),
or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl);

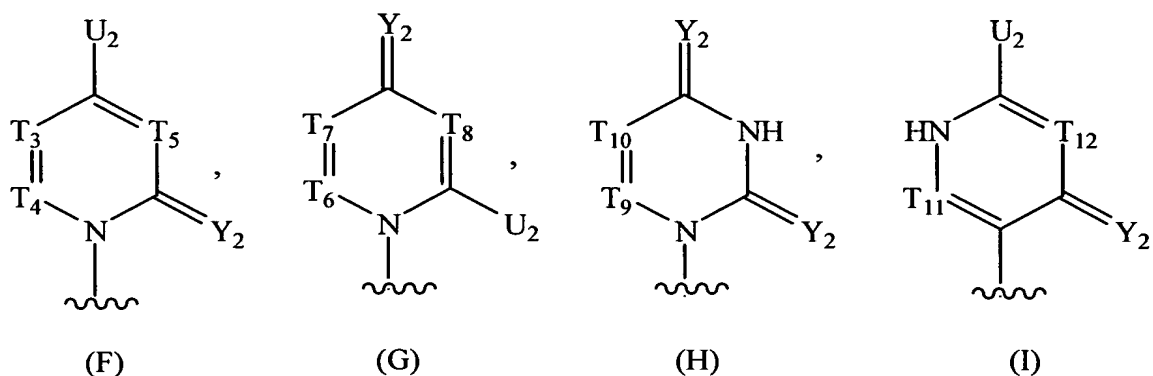
m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

Z is S, SO, SO₂, C=O, or NQ²⁰;

5 Q²⁰ is H or alkyl; and

V_1 and V_2 are independently selected from CH or N.

52. The method of claim 49, wherein base is of the formula:



10 wherein:

T_3 and T_4 are independently selected from N or CQ²²;

Q²² is independently selected from H, OH, substituted or unsubstituted alkyl,
substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl,
cycloalkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo,
15 OR⁴, NR⁴R⁵ or SR⁵, Br-vinyl, -O-alkyl, -O-alkenyl, -O-alkynyl, -O-aryl, -O-
aralkyl, -O-acyl, -O-cycloalkyl, NH₂, NH-alkyl, N-dialkyl, NH-acyl, N-aryl,
N-aralkyl, NH-cycloalkyl, SH, S-alkyl, S-acyl, S-aryl, S-cycloalkyl, S-
aralkyl, CN, N₃, COOH, CONH₂, CO₂-alkyl, CONH-alkyl, CON-dialkyl,
OH, CF₃, CH₂OH, (CH₂)_mOH, (CH₂)_mNH₂, (CH₂)_mCOOH, (CH₂)_mCN,
20 (CH₂)_mNO₂, (CH₂)_mCONH₂, C₁₋₄ alkylamino, di(C₁₋₄ alkyl)amino, C₃₋₆
cycloalkylamino, C₁₋₄ alkoxy, C₁₋₄ alkoxycarbonyl, C₁₋₆ alkylthio, C₁₋₆
alkylsulfonyl, (C₁₋₄ alkyl)₀₋₂aminomethyl, or -NHC(=NH)NH₂;

T_5 is NH;

R⁴ and R⁵ are independently selected from hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl);

m is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10;

T₆, T₇, T₈, T₉, T₁₀, T₁₁, and T₁₂ are independently selected from N or CH;

5 U₂ is H, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, OR⁴, NR⁴R⁵ or SR⁵;

Y₂ is O, S, NH, NR or CQ²⁴Q²⁶ where R is H, OH, or alkyl; and

10 Q²⁴ and Q²⁶ are independently selected from H, alkyl, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, OR⁴, NR⁴R⁵ or SR⁵.

53. A method for treating a patient infected with a *Flaviviridae* virus that is resistant to a 2'-branched nucleoside comprising administering an effective amount of interferon, optionally in a pharmaceutically acceptable carrier or diluent, optionally in a manner that substantially eliminates the viral load.

15 54. A method for treating a patient infected with *Flaviviridae* comprising:
administering an effective amount of a 2', 3' and/or 5'-prodrug of a 2'-branched nucleoside, or pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier or diluent;

20 in combination and/or alternation with one or more drugs that directly or indirectly induce a mutation in a *Flaviviridae* at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT, of domain B of the RNA polymerase region, and/or one or more drugs that are associated with such a mutation.

25 55. The method of claim 54, wherein the 2', 3' and/or 5'-prodrug of a 2'-branched nucleoside is a 2', 3' and/or 5'-prodrug of a 2'-branched pyrimidine nucleoside.

56. The method of claim 55, wherein the 2', 3' and/or 5'-prodrug of a 2'-branched nucleoside is 2', 3' and/or 5'-prodrug of β-D-2'-CH₃-riboC.

57. The method of claim 56, wherein the 2', 3' and/or 5'-prodrug of a 2'-branched nucleoside is 3'-amino acid prodrug of β -D-2'-CH₃-riboC.
58. The method of claim 57, wherein the 2', 3' and/or 5'-prodrug of a 2'-branched nucleoside is 3'-L-valinyl prodrug of β -D-2'-CH₃-riboC.
- 5 59. The method of claim 54 wherein the 2', 3' and/or 5'-prodrug of a 2'-branched nucleoside is a 2', 3' and/or 5'-prodrug of a 2'-branched purine nucleoside.
60. The method of claim 59 wherein the 2', 3' and/or 5'-prodrug of a 2'-branched nucleoside is 2', 3' and/or 5'-prodrug of β -D-2'-CH₃-riboA.
61. The method of claim 60 wherein the 2', 3' and/or 5'-prodrug of a 2'-branched
10 nucleoside is 3'-amino acid prodrug of β -D-2'-CH₃-riboA.
62. The method of claim 61 wherein the 2', 3' and/or 5'-prodrug of a 2'-branched nucleoside is 3'-L-valinyl prodrug of β -D-2'-CH₃-riboA.
63. The method of claim 59 wherein the 2', 3' and/or 5'-prodrug of a 2'-branched
15 nucleoside is 2', 3' and/or 5'-prodrug of β -D-2'-CH₃-ribo-6-N-methylamino-purine.
64. The method of claim 63 wherein the 2', 3' and/or 5'-prodrug of a 2'-branched nucleoside is 3'-amino acid prodrug of β -D-2'-CH₃-ribo-6-N-methylamino-purine.
65. The method of claim 64 wherein the 2', 3' and/or 5'-prodrug of a 2'-branched
20 nucleoside is 3'-L-valinyl prodrug of β -D-2'-CH₃-ribo-6-N-methylamino-purine.
66. A method for treating a patient infected with *Flaviviridae* comprising:
- (a) administering to the patient an effective amount of a 2'-branched nucleoside, or a pharmaceutically acceptable salt or prodrug thereof; optionally in a pharmaceutically acceptable carrier or diluent;
 - 25 (b) assaying the blood of the patient to test for seroconversion from wildtype to mutant virus;
 - (c) administering an effective amount of interferon; optionally in a pharmaceutically acceptable carrier or diluent.

67. A method for treating a patient infected with *Flaviviridae* comprising:
- (a) administering an effective amount of a 2'-branched nucleoside, or pharmaceutically acceptable salt or prodrug thereof; optionally in a pharmaceutically acceptable carrier or diluent;
 - 5 (b) obtaining a viral sample from the patient;
 - (c) determining the replication fitness of the virus;
 - (d) determining whether the replication fitness of the virus in the sample is less than the replication fitness of the wild-type virus, which indicates resistance to β -D-2'-CH₃-riboC;
 - 10 (e) administering an effective amount of interferon to those patients that are resistant to β -D-2'-CH₃-riboC.
68. A method for treating a patient infected with *Flaviviridae* comprising:
- (a) administering an effective amount of a 2'-branched nucleoside, or pharmaceutically acceptable salt or prodrug thereof; optionally in a pharmaceutically acceptable carrier or diluent;
 - 15 (b) obtaining a viral culture sample from the patient;
 - (c) culturing the sample and comparing the plaque growth between the sample and wild type virus;
 - (d) determining whether the plaque growth of the sample is smaller than the plaque growth of the wildtype, which indicates resistance to β -D-2'-CH₃-riboC;
 - 20 (e) administering an effective amount of interferon to those patients that are resistant to β -D-2'-CH₃-riboC.
69. The method of any one of claims 66-68, wherein the 2'-branched nucleoside is a 2'-branched pyrimidine nucleoside.
- 25 70. The method of claim 69, wherein the 2'-branched nucleoside is β -D-2'-CH₃-riboC.

71. The method of claim 69, wherein the 2'-branched nucleoside is a 3'-amino acid prodrug of β -D-2'-CH₃-riboC.

72. The method of claim 71, wherein the 2'-branched nucleoside is 3'-L-valinyl prodrug of β -D-2'-CH₃-riboC.

5 73. The method of any one of claims 66-68, wherein the 2'-branched nucleoside is a 2'-branched purine nucleoside.

74. The method of claim 73, wherein the 2'-branched nucleoside is β -D-2'-CH₃-riboA.

10 75. The method of claim 73, wherein the 2'-branched nucleoside is a 3'-amino acid prodrug of β -D-2'-CH₃-riboA.

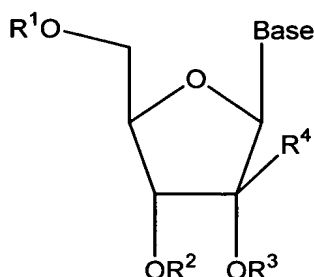
76. The method of claim 75, wherein the 2'-branched nucleoside is a 3'-L-valinyl prodrug of β -D-2'-CH₃-riboA.

77. The method of claim 73, wherein the 2'-branched nucleoside is β -D-2'-CH₃-ribo-6-N-methylaminopurine.

15 78. The method of claim 73, wherein the 2'-branched nucleoside is a 3'-amino acid prodrug of β -D-2'-CH₃-ribo-6-N-methylaminopurine.

79. The method of claim 78, wherein the 2'-branched nucleoside is a 3'-L-valinyl prodrug of β -D-2'-CH₃-ribo-6-N-methylaminopurine.

20 80. The method of any one of claims 66-68, wherein the 2'-branched nucleoside is of the formula:



or its pharmaceutically acceptable prodrug and/or salt, wherein

R¹, R², and R³ are independently H, phosphate (including mono-, di- or triphosphate and a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester (including alkyl or arylalkyl sulfonyl including methanesulfonyl); benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; lipid (including a phospholipid); amino acid; carbohydrate; peptide; cholesterol; or a pharmaceutically acceptable leaving group that provides a compound wherein R¹, R² or R³ is independently H or phosphate when administered *in vivo*; and

R⁴ is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chloro, bromo, fluoro, iodo, NO₂, NH₂, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)₂, or -N(acyl)₂;

and Base is a purine or pyrimidine.

81. A method for assaying a sample suspected of containing a *Flaviviridae* resistant to a 2'-branched nucleoside comprising:

(a) contacting a sample containing a *Flaviviridae* nucleic acid sequence with a detectable oligonucleotide probe having a sequence complimentary a codon that encodes a serine in the highly conserved consensus sequence, XRXSGXXXT, of domain B of the RNA polymerase region of *Flaviviridae*;

(b) allowing the probe to hybridize to the sequence;

(c) detecting the hybridization of the probe the sequence.

82. A method for assaying a sample suspected of containing a *Flaviviridae* resistant to a 2'-branched nucleoside comprising:

(a) contacting a sample containing a *Flaviviridae* nucleic acid sequence with a detectable oligonucleotide probe having a sequence complimentary to the cytidine at nucleotide 1214 of the RNA polymerase region of BVDV or the cytidine at nucleotide 8443 of HCV;

- (b) allowing the probe to hybridize to the sequence;
 - (c) detecting the hybridization of the probe to cytidine at nucleotide 1214 of the RNA polymerase region of BVDV or at nucleotide 8443 of HCV.
- 5 83. A kit for assaying a sample suspected of containing a *Flaviviridae* resistant to a 2'-branched nucleoside comprising:
 - 10 (a) a sample containing a *Flaviviridae* nucleic acid sequence with a detectable oligonucleotide probe having a sequence complimentary a codon that encodes a serine in the highly conserved consensus sequence, XRXSGXXXT, of domain B of the RNA polymerase region of *Flaviviridae*;
 - (b) a means for detecting the hybridization of the probe the sequence; and
 - (c) optionally with instructional material.
- 15 84. A kit for assaying a sample suspected of containing a *Flaviviridae* resistant to a 2'-branched nucleoside comprising:
 - 20 (a) a sample containing a *Flaviviridae* nucleic acid sequence with a detectable oligonucleotide probe having a sequence complimentary to the cytidine at nucleotide 1214 of the RNA polymerase region of BVDV or the cytidine at nucleotide 8443 of HCV;
 - (b) a means for detecting the hybridization of the probe to cytidine at nucleotide 1214 of the RNA polymerase region of BVDV or at nucleotide 8443 of HCV; and
 - (c) optionally with instructional material.
- 25 85. A method for diagnosing the presence of *Flaviviridae* resistant to a 2'-branched nucleoside in a patient comprising:
 - (a) obtaining a sample suspected of containing a *Flaviviridae* nucleic acid sequence;
 - (b) contacting the sample with a detectable oligonucleotide probe having a sequence complementary a codon that encodes a serine in the highly

conserved consensus sequence, XRXSGXXXT , of domain B of the RNA polymerase region of *Flaviviridae*;

(b) allowing the probe to hybridize to the sequence; and

(c) detecting the hybridization of the probe the sequence to determine the presence of a $\beta\text{-D-2'-CH}_3\text{-riboC}$ -resistant *Flaviviridae*.

86. A method for diagnosing the presence of a *Flaviviridae* resistant to a 2'-branched nucleoside in a patient comprising:

(a) obtaining a sample suspected of containing a *Flaviviridae* nucleic acid sequence;

(b) contacting the sample with a detectable oligonucleotide probe having a sequence complementary to the cytidine at nucleotide 1214 of the RNA polymerase region of BVDV or the cytidine at nucleotide 8443 of HCV;

(b) allowing the probe to hybridize to the sequence; and

(c) detecting the hybridization of the probe to cytidine at nucleotide 1214 of the RNA polymerase region of BVDV or at nucleotide 8443 of HCV to determine the presence of a $\beta\text{-D-2'-CH}_3\text{-riboC}$ -resistant *Flaviviridae*.